

nephrotic syndrome. (3) Loci rs5370 and 3A/4A are related to the plasma cholesterol level in NS children.

doi:[10.1016/j.lfs.2013.12.066](https://doi.org/10.1016/j.lfs.2013.12.066)

Evaluation of urinary and plasma endothelin-like domain peptide (ELDP) in chronic kidney disease

Jale Yuzugulen^a, Pajaree Lilitkarntakul^b, Elizabeth G. Wood^a, Robert A. Kimmitt^b, Neeraj Dhaun^b, Jane G. Goddard^b, David J. Webb^b, Roger Corder^a

^aWilliam Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, UK

^bBHF Centre of Research Excellence, University of Edinburgh, The Queens Medical Research Institute, Edinburgh, UK
E-mail address: j.yuzugulen@qmul.ac.uk (J. Yuzugulen)

Background: Current evidence indicates that endothelin-1 (ET-1) plays a physiological role in kidney collecting ducts by inhibiting Na⁺ reabsorption. Conversely, experimental models of renal disease suggest that ET-1 contributes to pathological processes by increasing vasoconstriction and stimulating fibrosis. ELDP is a recently identified EDN1 gene product (preproET-1 [93–166]) that is co-synthesised and co-released with ET-1. To investigate whether ELDP plays a role in the pathological changes occurring in chronic kidney disease (CKD), or may act as a biomarker for disease severity we assayed ELDP levels in urine and plasma samples from control subjects and patients with CKD. **Methods and results:** A specific double-recognition site sandwich ELISA for ELDP was optimised for urine and plasma measurements. Patients recruited to this study had renal disease without co-existing morbidities. Venous plasma and urine samples were collected after a 12 h fast and stored frozen at –80 °C until analysis. Plasma levels of ELDP (mean ± SD) were 6.34 ± 1.4 for control subjects and 6.16 ± 1.43, 7.01 ± 2.15, 7.74 ± 1.64, 8.96 ± 3.82 and 12.35 ± 4.45 pmol/L for CKD stages 1 to 5 respectively (P < 0.05 for the trend). Urine samples showed marked variation with no statistically significant pattern. Mean urine levels were 1.08 ± 1.19 pmol/L, with >200 fold difference between the minimum and maximum values of 0.03 and 6.65 pmol/L. **Conclusions:** The trend for increased plasma ELDP in patients with CKD adds further evidence to the concept that increased expression of EDN1 contributes to the vascular changes in these patients. The factors affecting urinary levels of ELDP merit further investigation.

doi:[10.1016/j.lfs.2013.12.067](https://doi.org/10.1016/j.lfs.2013.12.067)

Potential amelioration of upregulated renal HIF1alpha-endothelin 1 system through landiolol hydrochloride in a rat model of endotoxemia: A possible linkage to the increased renal vascular resistance based on renal microcirculation alteration in sepsis

Yoshiyasu Ogura, Nobutake Shimojo, Subrina Jesmin, Yoshimoto Seki, Hideaki Sakuramoto, Keiichi Hagiya, Satoru Kawano, Taro Mizutani

Department of Emergency and Critical Care Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
E-mail address: s0911688@u.tsukuba.ac.jp (Y. Ogura)

Alterations in the microcirculation in the renal cortex or renal medulla have been shown as a factor contributing to the development of renal dysfunction in sepsis despite normal or increased global renal blood flow (RBF). Sepsis-induced renal microvascular alterations (vasoconstriction, capillary leak syndrome with tissue edema, leukocyte and platelet adhesion with endothelial dysfunction

and/or microthrombosis) could contribute to an increase in renal vascular resistance in sepsis. Endothelin (ET)-1, a potent vasoconstrictor, has been implicated in the pathogenesis of sepsis and in our previous study we have shown that ET-1 is highly upregulated in renal tissues as well as in plasma after LPS administration and there is a potential imbalance in the renal tissue expression of vasoregulatory molecules. In the current study we investigated whether landiolol hydrochloride, an ultra-short-acting β-blocker, can play an important role in ameliorating the LPS-induced upregulated renal HIF-1alpha-ET-1 system with inflammatory cytokine (TNF-alpha) in a rat model of endotoxemia. Male Wistar rats at 8 weeks of age were administered lipopolysaccharide (LPS) for 3 h and some LPS-administered rats were continuously treated with landiolol for 3 h. At 3 h after LPS administration, both circulatory and renal TNF-alpha levels increased. In addition, LPS induced a significant upregulated expression of ET-1 and HIF-1alpha in the renal tissues compared to control. Finally, treatment of LPS-administered rats with landiolol for 3 h potentially normalized the upregulated renal TNF-alpha level as well as the HIF-1alpha-ET-1 system. These data taken together, led us to conclude that landiolol may be renal protective in endotoxemia modulating the renal microvascular alteration as well as renal vascular resistance.

doi:[10.1016/j.lfs.2013.12.068](https://doi.org/10.1016/j.lfs.2013.12.068)

p66 Shc mediates the effect of ET-1 on TRPC channel activity and changes in intracellular Ca2+ in renal vascular smooth muscle cells

Andrey Sorokin^a, Oleg Palygin^b, Bradley Miller^a, Alexander Staruschenko^b

^aDepartment of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

^bDepartment of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA

E-mail address: sorokin@mcw.edu (A. Sorokin)

Hypertension-induced nephropathy is accompanied by impaired renal vascular responsiveness and structural changes, but molecular mechanisms involved remain elusive. Elevation of intracellular Ca2+ ([Ca2+]i) is strongly linked to renal microvascular responses and is crucial for ET-1-induced contraction of smooth muscle cells (SMC). The adaptor protein p66 Shc is overexpressed in renal vascular SMC of hypertensive Dahl S rats. In patch clamp electrophysiology experiments carried out with primary SMCs isolated from renal vessels of zinc finger nuclease-mediated p66 Shc rat knockouts, we established that p66 Shc deficiency results in a dramatic increase in TRPC channel activity in response to ET-1. Knockout of p66 Shc resulted in the increase of channel activity. Next we showed that ET-1 produced dynamic changes in cytosolic Ca2+ concentration in SMCs derived from p66 Shc knockout rats, when compared with SMCs derived from their WT littermates. Fura 2-AM was used to measure changes in the [Ca2+]i before and after administration of 100 nM ET-1. We also tested activation of [Ca2+]i-dependent signaling pathways in renal SMCs isolated either from p66 Shc knockouts or from WT littermates. We have previously shown that ET-1-mediated activation of calcium regulated cytoplasmic tyrosine kinase Pyk2 caused an activation of p38 MAP kinase which is known to contribute to actin remodeling in SMC. Accordingly, we detected increased activation of Pyk2 and p38 MAP kinase in ET-1-treated SMCs isolated from p66 Shc knockout rats. Our data suggest that p66 Shc restrains activity of TRPC channels, which mediate influx of Ca2+ in SMC in response to ET-1, contributing to renal vascular dysfunction.

doi:[10.1016/j.lfs.2013.12.069](https://doi.org/10.1016/j.lfs.2013.12.069)